

In the Specification:

Please replace the paragraph at page 6, lines 8 through 14 with the following paragraph:

~~Figure 1~~ Figures 1A-1S show the amino acid sequence alignment of FATPs: mmFATP1 (SEQ ID NO:92), mmFATP2 (SEQ ID NO:93), mmFATP3 (SEQ ID NO:94), mmFATP4 (SEQ ID NO:95), mmFATP5 (SEQ ID NO:96), ceFATPa (SEQ ID NO:97), scFATP (SEQ ID NO:98) and mtFATP (SEQ ID NO:99). The underlining (amino acid residues 204-212 of mtFATP) indicates an AMP binding motif which is found in many classes of proteins; the underlining at amino acid residues 204-507 of the mtFATP sequence indicates the FATP 360 amino acid signature sequence.

Please replace the paragraph at page 8, lines 10 through 11 with the following paragraph:

~~Figure 26~~ Figures 26A-26E show the DNA sequence (SEQ ID NO:24) and predicted amino acid sequence (SEQ ID NO:25) of human FATP1.

Please replace the paragraph at page 8, lines 12 through 13 with the following paragraph:

~~Figure 27~~ Figures 27A-27D show the DNA sequence (SEQ ID NO:26) and predicted amino acid sequence (SEQ ID NO:27) of human FATP4.

Please replace the paragraph at page 8, lines 23 through 24 with the following paragraph:

~~Figures 30A and 30B~~ Figures 30A-30F show a comparison of the nucleotide sequence of human FATP1 (SEQ ID NO:28) and the nucleotide sequence of mouse FATP1 (SEQ ID NO:29).

Please replace the paragraph at page 8, lines 27 through 29 with the following paragraph:

~~Figures 31A and 31B~~ Figures 31A-31I show a comparison of the nucleotide sequence of human FATP4 (SEQ ID NO:30) and the nucleotide sequence of mouse FATP4 (SEQ ID NO:31).

Please replace the paragraph at page 9, lines 1 through 3 with the following paragraph:

~~Figure 32~~ Figures 32A-32C show a comparison of the amino acid sequence of human FATP1 (SEQ ID NO:32) and the amino acid sequence of mouse FATP1 (SEQ ID NO:33). Shaded amino acid residues match the ~~consensus~~ consensus sequence exactly.

Please replace the paragraph at page 9, lines 4 through 6 with the following paragraph:

~~Figure 33~~ Figures 33A-33C show human FATP4 (SEQ ID NO:34) and mouse FATP4 (SEQ ID NO:35). Shaded amino acid residues match the ~~consensus~~ consensus sequence exactly.

Please replace the paragraph at page 9, lines 7 through 8 with the following paragraph:

~~Figure 34~~ Figures 34A-34D show the nucleotide sequence (SEQ ID NO:36) and predicted amino acid sequence (SEQ ID NO:37) of hsFATP6.

Please replace the paragraph at page 9, lines 14 through 16 with the following paragraph:

~~Figure 36~~ Figures 36A-36G show an alignment of the amino acid sequences of hsFATP1 (SEQ ID NO:38), hsFATP4 (SEQ ID NO:39) and hsFATP6 (SEQ ID NO:40). Shaded amino acid residues match the ~~consensus~~ consensus sequence exactly.

Please replace the paragraph at page 9, lines 23 through 28 with the following paragraph:

~~Figure 39~~ Figures 39A-39C ~~is are~~ an illustration of the amino acid sequences of human FATP4 (SEQ ID NO:41) and mouse FATP4 (SEQ ID NO:42) compared to human FATP1 (SEQ ID NO:43). Shown by underlining are the FATP consensus sequence (236-556 of hsFATP1) and the AMP-binding motif (246-254 of hsFATP1). The human FATPs were cloned by screening libraries with sequences from ESTs (expressed sequence tags). Mouse FATP4 was cloned by PCR using degenerate primers.

Please replace the paragraph at page 10, lines 10 through 11 with the following paragraph:

~~Figure 43A~~ Figures 43A-43B ~~is show~~ the nucleotide sequence of the gene encoding mouse FATP4 (SEQ ID NO:44).

Please replace the paragraph at page 10, lines 12 through 13 with the following paragraph:

~~Figure 43B~~ Figure 43C ~~is shows~~ the amino acid sequence of mouse FATP4 protein (SEQ ID NO:45).

Please replace the paragraph at page 11, lines 14 through 15 with the following paragraph:

~~Figures 44A, 44B, and 44C are~~ 44A-44D show the hsFATP1 DNA sequence (SEQ ID NO:46). Coding region: 175-2115 (1941 nt).

Please replace the paragraph at page 13, lines 9 through 11 with the following paragraph:

~~Figures 94A and 94B~~ 94A - 94J are a representation of the DNA sequence (SEQ ID NO:101) of the hsFATP5 gene, and the amino acid sequence (SEQ ID NO:102) of the hsFATP5 protein.

Please replace the paragraph at page 21, lines 5 through 9 with the following paragraph:

One aspect of the invention relates to isolated nucleic acids that encode a FATP as described herein, such as those FATPs having an amino acid sequence in Figure 45 (SEQ ID NO:47), Figure 47 (SEQ ID NO:49), Figure 49 (SEQ ID NO:51), Figure 51 (SEQ ID NO:53), ~~Figures 94A and 94B~~ 94A-94J (SEQ ID NO:102), and Figure 55 (SEQ ID NO:57) and nucleic acids closely related thereto as described herein.

Please replace the paragraph at page 21, lines 10 through 26 with the following paragraph:

Using the information provided herein, such as a nucleic acid sequence set forth in ~~Figures 44A-44C~~ 44A-44D (SEQ ID NO:46), Figures 46A and 46B (SEQ ID NO:48), Figure 48 (SEQ ID NO:50), Figures 50A-50C (SEQ ID NO:52), ~~Figures 94A and 94B~~ 94A-94J (SEQ ID NO:101), and Figures 54A-54C (SEQ ID NO:56), a nucleic acid of the invention encoding a FATP polypeptide may be obtained using standard cloning and screening methods, such as those for cloning and sequencing cDNA library fragments, followed by obtaining a full length clone.

For example, to obtain a nucleic acid of the invention, a library of clones of cDNA of human or other mammalian DNA can be probed with a labeled oligonucleotide, such as a radiolabeled oligonucleotide, preferably about 17 nucleotides or longer, derived from a partial sequence. Clones carrying DNA identical to that of the probe can then be distinguished using stringent (also, "high stringency") hybridization conditions. By sequencing the individual clones thus identified with sequencing primers designed from the original sequence it is then possible to extend the sequence in both directions to determine the full length sequence. Suitable techniques are described, for example, in *Current Protocols in Molecular Biology* (F.M. Ausubel et al, eds), containing supplements through Supplement 42, 1998, John Wiley and Sons, Inc., especially chapters 5, 6 and 7.

Please replace the paragraph at page 22, lines 14 through 29 continuing at page 23, lines 1 through 11 with the following paragraph:

The invention further relates to nucleic acids (nucleic acid molecules or polynucleotides) having nucleotide sequences identical over their entire length to those shown in the figures, for instance Figures ~~44A-44C~~ 44A-44D (SEQ ID NO:46), Figures 46A and 46B (SEQ ID NO:48), Figure 48 (SEQ ID NO:50), Figures 50A-50C (SEQ ID NO:52), Figures ~~94A and 94B~~ 94A-94J (SEQ ID NO:101), and Figures 54A-54C (SEQ ID NO:56). It further relates to DNA, which due to the degeneracy of the genetic code, encodes a FATP encoded by one of the FATP-encoding DNAs, whose amino acid sequence is provided herein. Also provided by the invention are nucleic acids having the coding sequences for the mature polypeptides or fragments in reading frame with other coding sequences, such as those encoding a leader or secretory sequence, a pre-, or pro- or prepro- protein sequence. The nucleic acids of the invention encompass nucleic acids that include a single continuous region or discontinuous regions encoding the polypeptide, together with additional regions, that may also contain coding or non-coding sequences. The nucleic acids may also contain non-coding sequences, including, for example, but not limited to, non-coding 5' and 3' sequences, such as the transcribed, non-translated sequences, termination signals, ribosome binding sites, sequences that stabilize mRNA, introns, polyadenylation signals, and additional coding sequences which encode additional amino acids. For example, a marker sequence that facilitates purification of the fused polypeptide can be encoded. In certain

embodiments of the invention, the marker sequence can be a hexa-histidine peptide, as provided in the pQE vector (Qiagen, Inc.) and described in Gentz *et al.*, *Proc. Natl. Acad. Sci. USA* 86: 821-824 (1989), or an HA tag (Wilson *et al.*, *Cell* 37: 767 (1984)), or a sequence encoding glutathione S-transferase of *Schistosoma japonicum* (vectors available from Pharmacia; see Smith, D.B. and Johnson K.S., *Gene* 67:31 (1988) and Kaelin, W.G. *et al.*, *Cell* 70:351 (1992)). Nucleic acids of the invention also include, but are not limited to, nucleic acids comprising a structural gene and its naturally associated sequences that control gene expression.

Please replace the paragraph at page 23, lines 12 through 29 with the following paragraph:

The invention further relates to variants, including naturally-occurring allelic variants, of those nucleic acids described specifically herein by DNA sequence, that encode variants of such polypeptides as those having the amino acid sequences shown in Figure 45 (SEQ ID NO:47), Figure 47 (SEQ ID NO:49), Figure 49 (SEQ ID NO:51), Figure 51 (SEQ ID NO:53), Figures ~~94A and 94B~~ 94A-94J (SEQ ID NO:102), or Figure 55 (SEQ ID NO:57). Such variants include nucleic acids encoding variants of the above-listed amino acid sequences, wherein those variants have several, such as 5 to 10, 1 to 5, or 3, 2 or 1 amino acids substituted, deleted, or added, in any combination. Variants include polynucleotides encoding polypeptides with at least 95% but less than 100% amino acid sequence identity to the polypeptides described herein by amino acid sequence. Variant polynucleotides hybridize, under low to high stringency conditions, to the alleles described herein by DNA sequence. In one embodiment, variants have silent substitutions, additions and deletions that do not alter the properties and activities of the FATP. Allelic variants of the polynucleotides encoding hsFATP1 (Figure 45; SEQ ID NO:47), hsFATP2 (Figure 47; SEQ ID NO:49), hsFATP3 (Figure 49; SEQ ID NO:51), hsFATP4 (Figure 51; SEQ ID NO:53), hsFATP5 (Figures ~~94A and 94B~~ 94A-94J; (SEQ ID NO:102) and hsFATP6 (Figure 55; SEQ ID NO:57) will be identified as mapping to chromosomal locations listed for the corresponding wild type genes in Table 2 in Example 1.

Please replace the paragraph at page 24, lines 6 through 22 with the following paragraph:

The invention further relates to polynucleotides encoding polypeptides which are orthologous to those polypeptides having a specific amino acid sequence described herein, such as the amino acid sequences shown in Figure 45 (SEQ ID NO:47), Figure 47 (SEQ ID NO:49), Figure 49 (SEQ ID NO:51), Figure 51 (SEQ ID NO:53), Figures ~~94A and 94B~~ 94A-94J (SEQ ID NO:102), or Figure 55 (SEQ ID NO:57). These polynucleotides, which can be called ortholog polynucleotides, encode orthologous polypeptides that can range in amino acid sequence identity to a reference amino acid sequence described herein, from about 65% to less than 100%, but preferably 70% to 80%, more preferably 80% to 90%, and still more preferably 90% to less than 100%. Orthologous polypeptides can also be those polypeptides that range in amino acid sequence similarity to a reference amino acid sequence described herein from about 75% to 100%, within the signature sequence. The amino acid sequence similarity between the signature sequences of orthologous polypeptides is preferably 80%, more preferably 90%, and still more preferably, 95%. The ortholog polynucleotides encode polypeptides that have similar functional characteristics (e.g., fatty acid transport activity) and similar tissue distribution, as appropriate to the organism from which the ortholog polynucleotides can be isolated.

Please replace the paragraph at page 24, lines 23 through 28 continuing at page 24, lines 1 through 2 with the following paragraph:

Ortholog polynucleotides can be isolated from (e.g., by cloning or nucleic acid amplification methods) a great number of species, as shown by the sample of FATPs from evolutionarily divergent species described herein (see, e.g., Figures ~~44A-C~~ 44A-D through Figure 89). Ortholog polynucleotides corresponding to those in Figure 45 (SEQ ID NO:47), Figure 47 (SEQ ID NO:49), Figure 49 (SEQ ID NO:51), Figure 51 (SEQ ID NO:53), Figures ~~94A and 94B~~ 94A-94J (SEQ ID NO:102) and Figure 55 (SEQ ID NO:57) are those which can be isolated from mammals such as rat, dog, chimpanzee, monkey, baboon, pig, rabbit and guinea pig, for example.

Please replace the paragraph at page 25, lines 19 through 29 with the following paragraphs:

Further embodiments of the invention are nucleic acids that are at least 80% identical over their entire length to a nucleic acid described herein, for example a nucleic acid having the

nucleotide sequence in Figures ~~44A-C~~ 44A-44D (SEQ ID NO:46), Figures 46A-46B (SEQ ID NO:48), Figure 48 (SEQ ID NO:50), Figures 50A-50C (SEQ ID NO:52), Figures ~~94A and 94B~~ 94A-94J (SEQ ID NO:101), and Figures 54A-54C (SEQ ID NO:56). Additional embodiments are nucleic acids, and the complements of such nucleic acids, having at least 90% nucleotide sequence identity to the above-described sequences, and nucleic acids having at least 95% nucleotide sequence identity. In preferred embodiments, DNA of the present invention has 97% nucleotide sequence identity, 98% nucleotide sequence identity, or at least 99% nucleotide sequence identity with the DNA whose sequences are presented herein.

Please replace the paragraph at page 26, lines 1 through 10 with the following paragraphs:

Other embodiments of the invention are nucleic acids that are at least 80% identical in nucleotide sequence to a nucleic acid encoding a polypeptide having an amino acid sequence as set forth in Figure 45 (SEQ ID NO:47), Figure 47 (SEQ ID NO:49), Figure 49 (SEQ ID NO:51), Figure 51 (SEQ ID NO:53), Figures ~~94a and 94b~~ 94A-94J (SEQ ID NO:102) or Figure 55 (SEQ ID NO:57), or as such amino acid sequences are set forth elsewhere herein, and nucleic acids that are complementary to such nucleic acids. Specific embodiments are nucleic acids having at least 90% nucleotide sequence identity to a nucleic acid encoding a polypeptide having an amino acid sequence as described in the list above, nucleic acids having at least 95% sequence identity, and nucleic acids having at least 97% sequence identity.

Please replace the paragraph at page 27, lines 9 through 17 with the following paragraph:

The invention further relates to nucleic acids obtainable by screening an appropriate library with a probe having a nucleotide sequence such as that set forth in Figures ~~44A-C~~ 44A-44D (SEQ ID NO:46), Figures 46A-46B (SEQ ID NO:48), Figure 48 (SEQ ID NO:50), Figures 50A-50C (SEQ ID NO:52), Figures ~~94A and 94B~~ 94A-94J (SEQ ID NO:101) or Figures 54A-54C (SEQ ID NO:56), or a probe which is a sufficiently long fragment of any of the above; and isolating the nucleic acid. Such probes generally can comprise at least 15 nucleotides. Nucleic acids obtainable by such screenings may include RNAs, cDNAs and genomic DNA, for example, encoding FATPs of the FATP family described herein.

Please replace the paragraph at page 28, lines 6 through 13 with the following paragraph:

Further methods to obtain nucleic acids encoding FATPs of the FATP family include PCR and variations thereof (e.g., "RACE" PCR and semi-specific PCR methods). Portions of the nucleic acids having a nucleotide sequence set forth in Figures ~~44A-C~~ 44A-44D (SEQ ID NO:46), Figures 46A-46B (SEQ ID NO:48), Figure 48 (SEQ ID NO:50), Figures 50A-50C (SEQ ID NO:52), Figures ~~94A and 94B~~ 94A-94J (SEQ ID NO:101) or Figures 54A-54C (SEQ ID NO:56), (especially "flanking sequences" on either side of a coding region) can be used as primers in methods using the polymerase chain reaction, to produce DNA from an appropriate template nucleic acid.

Please replace the paragraph at page 30, lines 5 through 13 with the following paragraph:

The isolated proteins of the invention preferably include mammalian fatty acid transport proteins of the FATP family of homologous proteins. In one embodiment, the extent of amino acid sequence similarity between a polypeptide having one of the amino acid sequences shown in Figure 45 (SEQ ID NO:47), Figure 47 (SEQ ID NO:49), Figure 49 (SEQ ID NO:51), Figure 51 (SEQ ID NO:53), Figures ~~94A and 94B~~ 94A-94J (SEQ ID NO:102), or Figure 55 (SEQ ID NO:57), and the respective functional equivalents of these polypeptides is at least about 88%. In other embodiments, the degree of amino acid sequence similarity between a FATP and its respective functional equivalent is at least about 91%, at least about 94%, or at least about 97%.

Please replace the paragraph at page 75, lines 15 through 27 and continuing to page 79, lines 1 through 8 with the following paragraph:

To identify human cDNA clones encoding FATP family members, Millennium databases were searched for sequences similar to murine FATP1-5 coding regions. Two clones were analyzed in detail; inspection of the entire DNA sequence of these two clones showed that they encode the human orthologs of mmFATP1 and mm FATP4, respectively. These two clones were designated hsFATP1 and hsFATP4, and their DNA and predicted protein sequences are shown in Figures ~~44A-C~~ 44A-44D and 45, and 50A-50C and 51. hsFATP1 is predicted to encode a 646 amino acid, 71 kD protein with multiple membrane-spanning domains (Figure 28A). HsFATP4 is predicted to encode a 643 amino acid, 72 kD protein with multiple membrane spanning



domains (See Figure 29A). A comparison of the DNA sequences of mouse and human FATP1 and mouse and human FATP4 (Figures ~~30A-30B~~ 30A-30F and ~~31A-31B~~ 31A-31I) shows that the mouse and human orthologs are 85% (FATP1) and 87% (FATP4) identical to each other within the coding sequences given in these figures. At the amino acid level, hsFATP1 and hsFATP4 are ~90% identical to their respective mouse orthologs within the coding region shown in these figures (Figures ~~32-32A-32C~~ and ~~33-33A-33C~~). The sequence identities between mouse and human FATP1 and FATP4 are considerably higher than the ones observed between different FATP family members within one species (~40%-60%) and are present in the N-terminal part of the protein, a region that is poorly conserved between different FATP family members. This high degree of sequence conservation clearly demonstrates that the newly identified human FATPs are orthologs of mouse FATP1 and FATP4 rather than novel FATP family members.

Please replace the paragraph at page 76, lines 20 through 25 and continuing to page 77, lines 1 through 7 with the following paragraph:

A search of EST databases identified a set of overlapping human sequences that were similar to FATPs, but did not have a clear mouse ortholog. One of these EST clones was found to encode a full-length cDNA. The entire insert of this clone was sequenced and designated hsFATP6. The DNA and predicted protein sequences of hsFATP6 are shown in Figures 54A-54C and 55. HsFATP6 is predicted to encode a 619 amino acid, 70 kD protein with multiple membrane-spanning domains (Figure 35A). A comparison of the amino acid sequences of hsFATP6 with other human FATPs shows about 37% identity to either hsFATP1 or hsFATP4 (~~Figure 36~~ Figures 36A-36G). This degree of sequence identity is similar to what is observed between different mouse FATPs. The phylogenetic analysis described above clearly demonstrates that hsFATP6 is a member of the FATP family, but not an ortholog of any of the mouse FATPs. Comparisons were done with "ALIGN" (E. Myers and W. Miller, "Optimal Alignments in Linear Space," *CABIOS* 4:11-17 (1988) using standard settings.

Please replace the paragraph at page 85, lines 2 through 20 with the following paragraph:

Full-length clones encoding human FATP3 were identified by searching databases for sequences similar to the murine FATP1-5 coding regions using the BlastX algorithm (Altschul *et*

*al.*, *J. Mol. Biol.* 215: 403-410, 1990). Human clones with similarity to the 5' end of murine FATP sequences were sequenced completely. A clone encoding full-length human FATP3 was obtained from a human bone library constructed in the mammalian expression vector pMET7 (Tartaglia, L.A. *et al.*, *Cell* 83: 1263-1271, 1995). To identify human cDNA clones encoding FATP family members, databases were searched for sequences similar to murine FATP1-5 coding regions. One clone was found to encode the human ortholog of mmFATP3 and was designated hsFATP3. The DNA and predicted protein sequences of hsFATP3 are shown in Figures ~~94A and 94B~~ 94A-94J. hsFATP5 is predicted to encode a 703 amino acid 75.6 kD protein with multiple membrane-spanning domains. A comparison of the DNA sequences of mouse and human FATP3 shows that the mouse and human orthologs are 81% identical to each other within the coding region. At the amino acid level, hsFATP3 is ~86% identical to mm FATP3 within the coding region. The sequence identities between mouse and human FATP3 are considerably higher than those observed between different FATP family members within one species (~40%) and are present in the N-terminal part of the protein, a region that is poorly conserved between different FATP family members.